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CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT

A FATAL CASE OF POISONING WITH GB

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J.P. RUTLAND AND H. CULLUMBINE**

PORTON TECHNICAL PAPER No. 373

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PORTON TECHNICAL PAPER NO. 373

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DATE 9 - SEP 1953

A Fatal Case of Poisoning with GB

by

Major R.H. Adrian, G.L.D. Henderson^{*}, D.R. Davies,
J.P. Rutland and H. Cullumbine

SUMMARY

A case of fatal poisoning with GB is described. The clinical picture, autopsy findings and biochemical data are presented. Some suggestions for improving therapeutic measures are made.

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A Fatal Case of Poisoning with GB

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Introduction

During a trial with GB on human volunteers one of them (M) absorbed a fatal quantity of the agent. Despite immediate treatment his life could not be saved. This report records as fully as possible the circumstances and findings of the case.

1. The Clinical Picture

The trial, in the course of which M received a fatal intoxication, was one of a series designed to obtain a correlation between the inhibition of blood cholinesterase and the percutaneous dose of GB under various standard conditions. In this trial 6 volunteers were to have 20 x 10 mg. drops of pure GB placed on two layers of clothing over the forearm. Two groups, each of six men, had been similarly contaminated on April 29th and May 4th respectively. On neither occasion had any of the men complained of any symptoms or shown any signs of GB poisoning.

On May 6th six volunteers, who had not been used in any of the previous trials, entered a 100 cubic metre chamber with two experimental officers, who were to carry out the contamination. The air in the chamber was not circulated and the temperature was 74°F with a relative humidity of 58%. One of the authors was present as Medical Officer and was stationed outside the chamber observing the course of the trial through the glass windows.

Each man in the chamber was protected by a respirator (General Service type), the fitting of which had been tested in an atmosphere of CN. All were wearing heavy blue jean overalls over their normal clothing and a stockinette cap. These were normally removed immediately after the trial so that the subsequent hazard due to vapour absorbed on to clothing was reduced to a minimum. Some minutes before entering the chamber each of the volunteers had bared his left forearm and had had two pieces of cloth 12" x 7" tied loosely to the forearm. The inner layer of cloth was khaki flannel shirting and the outer layer khaki battledress serge.

On entering the chamber each volunteer went to a place at a table previously marked with his name, and one by one they were called to a second table where the contamination took place. Pure GB was drawn up into a pipette marked to deliver 10 mg. of the liquid. Twenty discrete drops each of 10 mg. (200 mg. total) were placed on the layers of cloth over the radial border of the left forearm of each man. The time at which each man was con-

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minated was noted. After contamination each man returned to his place, having been instructed to put his left forearm on the table in front of him. M, the fourth of the six, was contaminated at 10.17 hrs. and in exactly the same way as the five others. Each was to remain at his place for 30 minutes from the time of contamination. At the end of this time the contaminated cloth would be removed and he would be sent from the chamber.

At frequent intervals each man was asked how he felt. Up to twenty minutes after contamination M felt perfectly well but at twenty three minutes (10.40 hrs.) he said that he felt "pretty queer" and was seen to be sweating. He was immediately sent from the chamber accompanied by one of the experimental officers. His respirator and the contaminated cloth on his forearm were removed and he walked normally to a bench in the open air about 30 yards away. He was sweating but there was no miosis (as it was a bright sunny day the pupils were small, but not abnormally so). His pulse was full regular and of normal rate. He understood all questions and answered them coherently. Beyond feeling "queer" he had no specific symptoms. The ambulance was called (10.42 hrs.). About a minute later in response to a question M said that he could not hear though he appeared to realize that he was being spoken to. Fine tremors in his hands developed. The contents of two tubonic ampoules of atropine sulphate (2.4 mg. in all) were immediately injected into the median ante cubital vein. No difficulty was experienced with the injection as at this time convulsive movements of the arms had not started. A further 1.2 mg. atropine sulphate was given by intramuscular injection (3.6 mg. in all). As far as can be judged, M became unconscious very shortly after he said he could not hear. A tourniquet was not applied as, at the time, it was thought that whatever amount had penetrated had already been absorbed. Moreover, as explained in the discussion, intoxication to the degree which subsequently developed was totally unexpected.

While awaiting the arrival of the ambulance M was placed prone on the ground. His face was congested but the colour was good. Respiration became rapid, deep and laryngeal stridor developed. Profuse salivation did not occur nor did there seem to be much fluid secretion in the trachea. Tonic convulsive spasms developed at 10.44 hrs. shortly before the arrival of the ambulance at 10.45 hrs. These increased in frequency and strength until just before respiration ceased. When fully developed, with the patient prone on a stretcher, these were seen to consist of arching of the back and neck, so that the head was lifted from the pillow. The arms were abducted and flexed and externally rotated so that the clenched fists were pressed into the back of the neck. The buttocks were lifted from the stretcher probably as a result of attempted flexion of the hips and the knees were bent.

Just before the ambulance arrived breathing became, for a short period, shallower and slightly irregular. This however improved and oxygenation was well maintained. His pulse was regular and of about normal rate just before transfer to the ambulance.

During transfer to the Medical Centre, a distance of only about 600 yards the tonic spasms of back and limbs became stronger and laryngeal stridor more marked. In addition to the latter he cried out. These cries were involuntary, as he was unconscious, and were probably part of the general convulsive state.

On arrival at 10.47 hrs. at the Medical Centre, where the Establishment Medical Officer was waiting, he was transferred to a bed in the ward. Oxygen was administered by mask. The pupils were widely dilated. The pulse and colour were good. Shortly after this (10.50 hrs.) respiration became irregular, infrequent and gasping and finally ceased. He became cyanosed

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and artificial respiration was immediately started by Schaefer's method. A little mucus was cleared from his mouth and throat, though this was at no time troublesome. Initially artificial respiration was somewhat impeded by rigidity of the back and chest muscles but this passed off after a short time. Adequate respiratory exchange was achieved as his colour showed marked improvement. At no time after breathing had failed were there any signs of return of spontaneous respiratory activity. At 10.55 hrs. a further 1.2 mg. (in all 4.8 mg.) atropine sulphate was injected intravenously.

About five minutes later (11.00 hrs.) the patient's colour became ashen grey and he was incontinent of faeces. The pulse at the wrist could not be felt and the muscles were now completely relaxed. Anacardone (diethyl nicotinamide) was injected intramuscularly. The patient was placed on the floor and every effort to restore the circulation and respiration was made. The limbs were massaged towards the heart and the legs raised, hot water bottles were applied to the trunk and artificial respiration was maintained by manual methods combined with a bellows (positive pressure) resuscitator (P.T.P. 151). Judging by the movements of the chest and diaphragm adequate air entry was obtained but there was little improvement in colour and the pulse remained undetectable.

A further 4 x 1.2 mg. atropine sulphate (making a total dose of 9.6 mg.) were injected intramuscularly between 11.05 and 11.15 hrs. At 11.20 hrs. Anacardone was injected directly into the heart and this was repeated at 11.30 hrs. The arm pit temperature was 95.6°F at this time.

At 11.55 hrs. Anacardone was again injected (more deeply) into the heart and as a last resort one c.c. of liquid adrenalin was injected slowly into the heart whilst a watch was kept for returning action. No return of pulse was detected. Vigorous artificial respiration was maintained. At 13.30 hrs., after an electrocardiogram had showed that the heart was no longer beating, further treatment was abandoned.

At about 16.00 hrs. there was well developed rigor mortis in the jaw, back and legs; however the arms were flaccid. In this case, where there was considerable convulsive activity before death, the onset of rigor would be rapid. Its absence in the arms was probably due to stretching during undressing.

2. Autopsy Report

The body was that of a well built young male aged about 20 years.

The pupils were moderately dilated. Congestion and post mortem lividity was marked in the dependent parts. Marks of intravenous punctures were noted in the front of the left elbow and of an intracardiac injection in the front of the chest. The nail beds were cyanosed. No external evidence of injury was noted.

The skull was opened and the cerebrospinal fluid was noted to be in normal quantity and showed no evidence of blood-staining. The veins over the surface of the brain were moderately congested.

The tissues of the back were removed from the spinal column, the incisions revealing great congestion of the muscles.

The brain and cord were removed in one piece: no macroscopic evidence of disease or injury was noted. The circle of Willis and the vessels arising from it showed no evidence of disease. Macroscopic section of the cerebrum, mid and hind brain and the cerebellum showed no abnormality.

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On opening the neck, the thyroid was removed and a clamp placed over the trachea.

Thyroid 21.6 g. (Normal - 40 g.) Normal in appearance.

Thymus 32 g.

The pleural cavities were free from any excess of pleural fluid. Both lungs were normally expanded. The diaphragm was at its normal level.

The larynx was normal. The trachea and bronchi were reddened and contained much thick viscid mucus in which was embedded some granular material. In the smaller bronchi complete obstruction had been produced by the mucus. Both lungs were congested and slightly oedematous, the right upper lobe showing a free flow of fluid from the cut surface.

Left lung 565 g. (Normal Left 420 - 600 g.)

Right lung 650 g. (Normal Right 480 - 600 g.)

The mucus from the bronchi contained desquamated epithelial cells and a few gran positive organisms. The granular material appeared to be talc. (It gave negative results with tests for aspirin and bismuth: it was doubly refractile when viewed through crossed polarising screens). Culture yielded an almost pure growth of streptococcus viridans, with a few staphylococcus albus.

The pericardium was congested. A small needle puncture wound was noted passing into the interventricular septum. The pericardial fluid was blood-stained. A few Tardieu's spots were present under the visceral pericardium.

Both coronary arteries were free from any obstruction: a few very small flecks of atheromatous degeneration were present in both vessels. The heart muscle, valves and endocardium were all normal. The aorta presented an occasional very small fleck of atheroma along its whole length.

Weight of heart 398 g. (Normal 270 - 360 g.)

Abdomen - The mesentery, the lesser omentum and the gastrosplenic and phrenico-splenic ligaments were thickened by a jelly like fluid lying between the two layers of peritoneum. A small excess of pleural fluid was present.

The bladder contained clear, pale yellow urine of which 180 cc. were measured. The ureters were normal. Prostate small and soft.

Liver 2,160 g. (Normal 1400 - 1700 g.)

Kidneys, left 158 g. (Normal 150 g.)

right 153 g. (Normal 140 g.)

Spleen 240 g. (Normal 150 - 200 g.)

Adrenals, right and left 8 g. each (Normal 3 - 6 g.)

were very congested but otherwise macroscopically normal.

The oesophagus was normal.

The stomach and duodenum contained bloody fluid in which was found further granules of talc. The walls of these viscera were intensely congested, with many minute points of haemorrhage. No ulcer was noted. A small gland was removed from the epiploic fold of lesser omentum: several soft glands were found in the mesentery. The rest of the bowel was normal and showed no spasm.

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The vertebrae were noted to be of normal consistency.

Skin and underlying muscle samples were taken from the front of both forearms, together with the left submaxillary gland.

Post Mortem Urine:

Specific gravity	1020
Reaction	alkali to litmus
Sugar	Nil
Albumen	heavy cloud
	1.8 g./litre (Esbach's method)

Deposit

- Amorphous phosphates
- Numerous epithelial cells
- Occasional leucocytes and red blood cells
- One leucocytic cast

Histological examination of the tissues showed no evidence of pre-existing disease.

The congestion, dark cyanosis of the blood which was fluid, the presence of Tardieu's spots and of oedema indicate an asphyxial death. This is explained by the blocking of the bronchi by the thick, viscid mucus which was present in such large quantities.

No evidence of disease or injury was revealed which would account for death or for the production of this fluid.

The appearances are compatible with those which would be found by overaction of the parasympathetic nervous system or by reduction in cholinesterase.

3. Biochemical Findings

Technique

The tissues which were examined were obtained within three hours of autopsy and twenty four hours after death. Estimations of cholinesterase were made upon homogenates of the tissue in M sodium bicarbonate, using the Warburg manometric technique. Skin was an exception in that thin slices of the frozen tissue were used.

Acetyl choline (ACh) 0.015M, acetyl- β methyl choline (MCh) 0.03M, and butyryl choline (BuCh) 0.03M were the substrates employed.

The amount of tissue used in each estimation depended upon the actual tissue and varied from 0.2 gram in the case of the skin to 0.05 gram with brain tissue.

Normal data existent in the literature are expressed as the volume of carbon dioxide in microlitres produced in 1 hour by one gram of tissue. Our observations were standardised for a half hour period only; all the observed results had therefore to be multiplied by a conversion factor of between 10 and 60, again depending upon the tissue. Such a conversion will of necessity exaggerate differences.

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The Assessment of Inhibition

The absence of adequate normal data tends to make any precise assessment of inhibition extremely difficult. Data from the literature are available from only a few authors (Ord and Thompson 1953, Grob 1949, Nachmansohn 1939, Thompson and Whittaker 1942 and Longemann 1944). With one exception, the authors have not attempted to define normal limits of esterase activity, and the reports are rather in the nature of attempts to classify the type and distribution of cholinesterase present in the tissues. The exception, Grob, studied variation in a series of eight normals in order to interpret the findings he had made in a case of fatal poisoning with parathion. Grob's figures, however, do not compare with either those of Ord and Thompson or Nachmansohn, nor indeed do Ord and Thompson's and Nachmansohn's figures compare (see Table 1).

Table 1

Normal Values of the Cholinesterase Activity of Various Parts of the Brain μl CO ₂ /g/hr.								
Author	Lentiform Nucleus		Caudate Nucleus		Cerebellum		Cortex	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Ord and Thompson (1952)	24,650		16,900		4,540		-	
Grob (1949)	-		-		19,900	(9000-30,000)	4000	(1600-9,000)
Nachmansohn (1939)	57,000		37,000		20,000		1500	
Longemann (1944)								

The reason for the marked discrepancies between these various authors is not clear, but they may well be due to gross differences in technique. For this reason we have used Ord and Thompson's normal data for comparison, since our technique was very similar to theirs.

The Cholinesterases of the C.N.S.

The enzymes in the lentiform and caudate nuclei, the cortex and the spinal cord were determined. The results are shown in Table 2.

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Table 2

The Cholinesterases of the Central Nervous System

Tissue	ACh	M:Ch	BuCh	Normal value - ACh
Lentiform Nucleus	4,720	1,620	475	24,650 ^x
Caudate Nucleus	2,300	1,464	368	16,900 ^x
Cerebellum	612	474	526	4,540 ^x
Cortex	37	-	-	3,990 ^o
Spinal Cord	108	-	-	
<div style="display: flex; justify-content: space-between; padding: 0 10px;"><div>x Normal values after Ord and Thompson</div><div>o " " " Longemann</div></div>				

Against the background of Ord and Thompson's normal data, it would appear that the acetyl choline splitting power of these tissues had been inhibited by about eighty per cent. This means that the combined activities of the true and pseudo esterases had been so reduced. Measurements with M Ch and BuCh, which characterise the true and pseudo esterases respectively, permit us to obtain some idea of how the two enzymes had been attacked separately. Thus, Ord and Thompson showed that MCh is hydrolysed by normal human brain tissue at about 65-70 per cent of the rate at which ACh is hydrolysed. In the case of the lentiform nucleus which breaks down ACh at 25,000 $\mu\text{l CO}_2/\text{g/hr.}$ the precise factor for M Ch is 72 per cent, giving a normal figure for M Ch hydrolysis of approximately 17,500. The activity of the specimen examined was 1,700 $\mu\text{l CO}_2/\text{g/hr.}$, i.e. only about ten per cent of the normal activity remained.

Applying the same argument to the pseudo esterase activity, the normal figure is about 1,500 and the activity in the sample 500. Thirty per cent of the pseudo cholinesterase remained inactivated. A similar sort of picture emerges with the other tissues, namely, that the "true enzyme" had been almost completely inhibited, whilst the pseudo esterase content remained relatively active. This picture is not inconsistent with our experience with human blood where the red cell or true enzyme tends to be more inhibited by GB than the plasma or pseudo cholinesterase.

The spinal cord cholinesterases were also investigated. No normal data were however available. The extremely low value of 108 $\mu\text{l CO}_2/\text{g/hr.}$ found for this tissue suggests that marked inhibition had occurred.

The Cholinesterases of the Skin and Muscles of the Arms

Since poisoning occurred as a result of the application of GB to the skin of the left forearm, the levels of the esterase of the skin and muscle at the point of application compared with those on the opposite or control arm are informative.

Unfortunately normal data for these tissues are extremely limited. Thompson and Whittaker quote values for two samples only of human skin. No data are available for muscle.

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If however the activities of the tissues on the left and right arms are compared it is possible to hazard a guess at the mode of penetration of the agent through the skin. The activities are recorded in Table 3.

Table 3

The Cholinesterases of the Skin and Muscle of the Arms

Tissue	Site	Activity against ACh	Normal Value
Skin	Left forearm	70	490
Skin	Right forearm	190	-
Muscle	Left arm	558	-
Muscle	Right arm	650	-

Normal value after Thompson and Whittaker

From this table it is seen that the skin of the left arm is less active than the right. In fact the right arm is two and half times as active as the left, and this suggests that a certain amount of localised inhibition has occurred. What is perhaps surprising is that any activity still remained, since on the basis of Thompson and Whittaker's figures, the activity observed would be about fifteen per cent of normal. On this basis the skin on the right arm too appears to be significantly inhibited, indicating a generalised effect which is distinct from the local one referred to above.

The muscle of both arms seems to be equally active. This observation is difficult to interpret in the absence of normal data. If, however, inhibition has occurred, then it must be due to the generalised reaction which is seen in nearly all the other tissues, rather than to a highly specific local effect. If this interpretation is correct, then a picture of the process of intoxication emerges. The GB first tends to inhibit some of the skin esterases, but even before this process is complete, the agent is drained away by the capillary blood supply and very little is at that period absorbed by the tissues immediately under the skin. The inhibition of the esterases of the muscle would thus be a general systemic effect rather than the consequence of local action. The rapid lethal action of the agent under these conditions and in such small doses could thus be explained. This hypothesis could easily be examined more closely by more controlled animal experiments.

The Cholinesterases of Other Tissues

No normal data upon the levels of cholinesterase activity in the intestinal tract are available. In other species, however, the gastric mucosa is very rich in pseudo cholinesterase (Ord and Thompson, Davies, Risley and Rutland). If human tissues are similar, then the mucosa esterase had undoubtedly been markedly inhibited. The muscles of the stomach and duodenum appeared by comparison with other species to have been relatively little inhibited.

The activities of the spleen, kidney and pancreas were all markedly reduced and would appear to have suffered a ninety per cent inhibition. The submaxillary gland, however, was only inhibited by about seventy per cent.

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The lung and heart ventricle esterases, rather surprisingly, did not seem to be very markedly reduced. The estimates of inhibition are, however, based upon normal values the reliability of which it is rather difficult to assess, and their apparent departures from a general picture of extensive inhibition in the other tissues should be accepted with caution.

Table 4
The Cholinesterases of Other Tissues

Tissue	Substrates			Normal Values A.Ch
	A.Ch	M.Ch	BuCh	
Stomach				
Muscle	838	155	658	-
Mucosa	355	155	603	-
Duodenum				
Muscle	600	0	496	-
Mucosa	313	-	-	-
Liver	580	55	1060	-
Kidney	92	-	-	1344 °
Spleen	279	-	-	3220 †
Pancreas	423	-	-	1880 †
Submaxillary G.	94	-	-	-
Thyroid	232	-	-	-
Thymus				
Heart	150	-	-	107 †
Lung	710	-	-	1500 †

† Normal values after Grob

° Normal values after Langemann

Some comment upon the activity of the liver is necessary, since the activity of the specimen towards BuCh was so much greater than towards ACh, and particularly since ACh activity suggests a ninety per cent destruction of the cholinesterase. If the enzyme in the liver is wholly pseudo cholinesterase, no discrepancy exists for Davies et al have shown that the pseudo enzyme of human plasma hydrolyses BuCh at twice the rate that it hydrolyses ACh. A similar explanation accounts for the relatively high BuCh figure which is seen with the mucosa of the stomach.

Discussion of biochemical findings

The general pattern of the biochemical findings in this case is regular in that a marked inhibition of the cholinesterases of nearly all tissues of the order of eighty or ninety per cent was observed. Furthermore, studies involving the use of specific substrates show that, in the C.N.S. at least, the true enzyme was preferentially attacked.

It is unfortunate that so little information upon the normal levels of skin and muscle are available, since a clearer picture of the relative inhibition of the enzymes of these tissues might have provided a more precise demonstration of the manner of skin penetration.

The difficulties of interpretation consequent upon the lack of normal data have been pointed out above, and it is again stressed that the detailed

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estimates of inhibition should be accepted with reserve. Even with this caveat, however, there is no doubt that the cholinesterases of the tissues examined had been very extensively inhibited.

4. General Discussion

This fatal incident is an extreme example of the possible wide variation in individual response to cutaneous liquid contamination with GB. Up to and including the group of subjects of whom M was a member, a total of 396 men had been contaminated with varying doses of liquid GB. Of this number, the following had received contaminations equal to or greater than that received by M:-

<u>Dose - mg.</u>	<u>Number</u>	<u>Contamination on</u>
200	30	Bare skin
	20	1 layer of serge
	18	1 layer of serge and 1 layer of flannel.
250	24	Bare skin
	19	1 layer of serge
300	45	Bare skin
	26	1 layer of serge

Five of these subjects were hospitalized for vomiting and one for apnoea and convulsions (see P.T.P. 361). The latter received 300 mg. through one layer of battle-dress serge, and because of this experience the contamination applied was reduced to 200 mg. and a second layer of clothing was interposed between the liquid GB and the skin. Eighteen men were contaminated in this fashion; one of these was M, the other 17 showed no signs or symptoms of G intoxication.

Why M should have died with typical clinical and pathological signs of G poisoning and the others should have been unaffected is not known. M had no clinical skin abnormality and no abrasions at the site of contamination. The pieces of serge and flannel placed on his forearm were cut from the same rolls of cloth as the pieces used for the other volunteers and were not detectably different from them. He showed no evidence of pre-existing disease and his pre-exposure blood cholinesterase content was within normal limits, viz:-

Red Cell ChE (units)

	<u>Manometric</u>	<u>Electrometric</u>
M.	116	79
Normal Mean	112	80
Normal 5% limits	92-132	63-97

It is highly improbable that a respirator leak was present, as miosis, headache, etc. would then have been the initial events; moreover the respirator had been carefully fitted and tested in an atmosphere of CN.

Cholinesterase determinations on post-mortem blood from M gave the following values:-

Red Cell ChE

	<u>Units</u>	<u>% Inhibition</u>
Manometric	8	93
Electrometric	1	99

The percentage inhibitions of red cell ChE produced in the other 17 volunteers were:

Subject	Per Cent ChE (red cell) Inhibition		Subject	Per Cent (red cell) Inhibition	
	Manometric	Electrometric		Manometric	Electrometric
R ₁	28	32	E ₂	34	23
J ₁	29	20	W ₁	50	43
T ₁	22	17	W ₂	42	30
C ₁	27	35	J ₃	47	32
E ₁	10	13	V ₁	83	80
J ₂	17	32	N ₁	56	51
P ₁	43	38	G ₁	52	49
H ₁	19	11	C ₂	54	53
S ₁	90	84	-	-	-

The marked variation in extent of ChE inhibition in different subjects receiving the same degree of contamination has been typical of the results obtained throughout the whole of the investigation. The factors determining the varying blood ChE responses of different individuals are not known. Within the normally accepted range of ChE values, the pre-contamination level of ChE is not a guide and the absolute loss of ChE units of activity following contamination is no better correlated to dosage than the ChE percentage inhibition.

On the basis of an estimated intravenous LD50 for man of 20 µg./kg. the contamination of 200 mg. GB represents 140 intravenous LD50's. Comparatively small variations in absorptions might, therefore, encompass the lethal dose and the physiological factors controlling skin absorption and clearance from the dermis will be important in determining the individual response. Experiments with GB and TEPP, tagged with dyes or radioactive P, show that penetration may occur readily through the hair follicles and much more slowly through the intact epidermis. Both penetration and clearance follow an exponential pattern and wide variations in penetration rate are shown by different subjects. The skin temperature, from our limited observations, does not seem to be important.

The various factors which may influence skin absorption are being studied.

There can be little doubt that M did in fact absorb a lethal quantity of GB. It remains to discuss the immediate cause of death and the reasons for failure of treatment. It is our opinion that death was caused by failure of the heart at, or shortly after, 11.00 hrs.

It has been suggested (Wood 1950) that atropine given during the period of anoxia following cessation of respiration might lead to ventricular

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fibrillation due to sudden release from vagal tone. It is felt that in this case, as intravenous atropine was administered first 5-7 minutes before apnoea, the intravenous atropine administered at 1055 could not have produced fibrillation. However, the assumption that intravenous atropine is desirable should be investigated further.

From the time that respiration ceased until the time of the apparent circulatory collapse, vigorous manual artificial respiration and oxygen by mask improved the patient's colour. Oxygenation during this period must therefore have been adequate. We are therefore at a loss to explain the sudden deterioration, leading to death, in the patient's condition at this time. That the atropine administered was in fact absorbed promptly is indicated by the fact that at no time was salivation prominent, in fact his mouth was seen to be very dry.

Initially, at least, while convulsive muscular spasms were still present artificial respiration was somewhat hindered by rigidity of the muscles of the chest wall. This passed off later and with the bellows resuscitator adequate movement of the chest was obtained. At post mortem the smaller bronchi were found to be completely blocked by very thick viscid mucus but it is difficult to judge to what extent this may have been forced there by positive pressure ventilation carried on after death.

The bellows resuscitator which was an experimental prototype designed for emergency use, was found to have several drawbacks when used under the circumstances in this case. There was no attachment by which oxygen could be administered and the seal of the face piece could not be made adequate with the face to one side. With the patient prone and the face upwards, the tongue and jaw tended to obstruct the air way. This could be overcome by a tongue clamp (which again interferes with the seal of the face piece), a stitch through the tongue or an anaesthetic air way. Tracheal intubation, in the presence of marked laryngeal spasm would have been difficult, and at later stages the time involved might have been critical. The factor which hindered adequate oxygenation to the greatest extent would appear to have been, however, the blocking of the medium and smaller bronchi with mucus.

Whether a tourniquet applied to the contaminated limb would have helped in this incident cannot, of course, be stated. In P.T.P. 243 it has been reported that restricting the circulation from a rabbit's limb is effective in reducing the mortality from a large cutaneous dose of GB. In this series of rabbit experiments the longest time interval between contamination and the application of a tourniquet was 2 minutes. Here 23 minutes had elapsed before the first symptoms occurred, and, by this time, a fatal dose of GB had probably been absorbed into the body generally. This does not rule out entirely the possibility that a tourniquet might have prevented further intoxication. It should therefore be considered whether, whenever accidental contamination of a limb occurs, it should be made a standard feature of first aid treatment to apply a tourniquet at once, or in experiments similar to these, at the first sign or symptom appearing.

The post mortem examination findings were those of asphyxial death and this was attributed to the blocking of the smaller bronchi with viscid mucus. As explained previously this could have been exaggerated by post mortem positive pressure ventilation. The congestion of the abdominal viscera was extreme and the stomach contained a thick fluid with altered blood. The mucosa showed many small points of haemorrhage which might have been due to the intense

congestion, and possibly, in addition, compression of the lower chest in artificial respiration. The presence of talc in the trachea can be explained by the fact that talc was applied to the external rubber parts of the bellows mechanism as these had become very sticky.

Three cases of severe poisoning with GB have now been reported viz., one following exposure to GB vapour (Clanton and Ward, 1953) and two following liquid GB contamination (Cullumbine, 1953 and this report). In each a lethal or near-lethal dose of GB must have been absorbed and some idea of the clinical picture following such an absorption can now be presented.

The onset of symptoms is sudden and the initial symptom seems to be a feeling of faintness (e.g. "giddy", "faint", "queer") probably associated with cardio-vascular collapse. This faintness may be accompanied by a staggering gait, muscle tremors and massive sweating and is rapidly followed by the complete collapse of the subject into unconsciousness. (A matter of 1-3 minutes, as far as can be judged, was the maximum period in each case between the first symptom and this collapse).

Convulsive spasms involving all the skeletal musculature then develop. These continue for a period which varies from patient to patient (1 minute, 12 minutes, 30 minutes) and cease as flaccid paralysis develops.

The respiration is at first somewhat rapid, deep but regular and is accompanied by a laryngeal stridor. Later the breathing becomes shallower and irregular, with periods of apnoea, before ceasing altogether. Broncho-constriction seems to be slight but considerable resistance to air movement occurs due to the excessive secretion of thick mucus in the respiratory passages.

The occurrence of symptoms is much more rapid following vapour exposure (about 10 seconds) than after liquid contamination of the clothed skin (more than 30 minutes; 25 minutes). It is interesting to note that J.A. "detected a faint odour" when breathing the vapour. This subject also exhibited pin-point pupils, whereas wide dilation of the pupils was seen following the liquid skin contamination.

The clinical description in all three cases is not that of simple GB poisoning since therapy was applied early in each case. Further, the amounts absorbed must have been different, the route of intoxication varied and the therapy routine was altered to suit each case. Therefore precise parallelism in the details of the clinical history of each patient cannot be expected. Nevertheless the above composite description, with the sequence of sudden faintness, collapse, convulsions, flaccid paralysis, respiratory failure and a continuous impediment to ventilation due to excessive secretions in the respiratory tract, does show the main crises which were common to all three incidents.

When recovery occurs it is almost as dramatic as the onset of symptoms and when full and prolonged atropinization has been possible as in these cases, convalescence is rapid and the after-symptoms are mild. These latter consist of nausea and vomiting, especially on drinking fluids, lethargy (maybe due to the atropine or the GB), and, following vapour exposure, photophobia, headache and blurred vision.

Some general remarks on therapy based on the experiences from these three cases can also be presented for future consideration.

(1) First Aid Treatment:- The symptoms commence suddenly and are vague. It is doubtful whether J.A., following his vapour exposure, could have prepared his atropine self-injection device and injected himself in the time between recognising his symptoms and his collapse. The liquid contaminated men had relatively more time but whether they could have injected themselves is not certain. The answer must be based upon the ease of recognition and the specificity of their symptoms. However there was a long latent period of many minutes between contamination and the onset of symptoms. If the contamination is recognised, presumably, the instructions in the field will be removal of contaminated clothing, decontamination and atropine self-injection.

(2) Convulsions:- These will interfere with early intravenous therapy and with many manual methods of artificial respiration.

(3) Positive Pressure Resuscitator:- Such a device proved valuable for the emergency ventilation of the vapour case and also gave good ventilation in the fatal contamination case. Its use would now seem, therefore, to be justified on theoretical, experimental (Muir, Calloway and Cullumbine, 1952) and clinical grounds. One possible danger attending its use can, however, now be stated. This is the possibility that the thick mucous secretions in the airway may be forced down into the smaller bronchi and so produce a block to ventilation. The likelihood of this occurring should be investigated.

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References

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| Ainsworth and Truckle | P.T.P. 243 |
| de Candole | P.T.P. 151 |
| Cullumbine | P.T.P. 361 |
| Clanton and Ward | M.L.R.R. Rept. 151 |
| Davies, Risley and Rutland | P.T.P. 306 |
| Grob | Quarterly Prog. Rep't., Cont. W-49-057-CWS-48, Oct. 1st, 1949. |
| Langemann | Helv. Physiol. Acta. 1944, 2, 367 |
| Muir, Calloway and Cullumbine | P.T.P. 300 |
| Nachmansohn | Bull. Soc. Chim. Biol. 1939, 21, 761 |
| Ord and Thompson | Biochem. J. 1952, 51, 245 |
| Thompson and Whittaker | Biochem. J. 1944, 38, 295 |
| Wood | J. Amer. Med. Ass. 1950, 144, 8 |

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